



Clinical trial challenges – impact of the new clinical trial regulation on the conduct of clinical trials

Izazovi u kliničkim ispitivanjima – uticaj nove uredbe na sprovođenje kliničkih ispitivanja

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Introduction

Clinical trials are very important for the development of new therapeutic options. The current high standards in medical practice can be attributed to the large number of clinical trials that have been conducted so far. Without clinical trials, there is no progress in medicine and, more broadly, the survival of humanity. Therefore, the aim is to provide appropriate regulation of clinical trials.

In Europe, the largest number of clinical trials is conducted in Western European countries, and the total number of applications for authorization of clinical trials of medicines [Clinical Trial Application (CTA)] across Europe decreased by 25% in the period from 2007 to 2011¹. This allowed linking the issue to the potentially problematic provisions of the current EU Clinical Trial Directive No 2001/20/EC^{2,3}. Due to a certain unfavorable impact of reduced activity in the field of clinical trials on public health, several initiatives were launched to encourage the conduct of clinical trials, and finally, it was time to introduce a new Regulation.

The Clinical Trial Regulation No 536/2014 was published in the Official Journal of the European Community on May 27, 2014⁴. The Regulation was adopted to fortify Europe's attractiveness for clinical trials and provide a favorable environment for conducting clinical trials, thus facilitating access to new therapeutic methods while promoting the rights and safety of clinical trial subjects. The Regulation will repeal the existing Directive and become applicable in Europe when the Clinical Trials Information System (CTIS)

and database maintained by the European Medicines Agency (EMA) become ready for deployment, which should happen towards the end of 2021^{4,5}.

Regulatory development overview

The current essential document for clinical trials application is Directive 2001/20/EC, adopted by the European Parliament and the Council of the European Union on April 4, 2001, and implemented on May 1, 2004³. Prior to the entry into force of the Directive, there were different processes and requirements for clinical trial authorizations in the EU Member States (MS), which resulted in “delays and complications detrimental to effective conduct of clinical trials” in EU³.

Thus, the Directive was the first attempt to harmonize the process of authorization of clinical trials. It is based on the World Medical Association Declaration of Helsinki Ethical Principles for Medical Research Involving Human Subjects 1964, International Conference on Harmonization (ICH) guidelines, and good clinical practice guidelines drafted in 1990 by the European Commission³. The Directive was seen as a step towards greater transparency and making new medicines more accessible to patients without compromising their safety. However, there were concerns expressed soon after its implementation⁶. Even though the Directive must be acknowledged for the numerous benefits it has brought, which are primarily reflected in greater safety of subjects, better communication between sponsors and researchers, as well as greater reliability of data and thus clinical

cal trial results, its provisions issued many problems^{7, 8}. Numerous weaknesses have been identified, including different interpretations of the provisions, different concepts of approval in the MS, divergent assessments regarding the same studies, different timelines, different outcomes, poor reporting concepts, etc.^{2, 6, 9}. As a matter of fact, a survey conducted by Applied Clinical Trials (ACT) and SCORR Marketing in 2015, which included individuals from different types of companies, including, in part, drug sponsors, contract research organizations, academic institutions, consultancies, and service providers, confirmed negative attitudes about the impact of the Directive on clinical trials and drug development¹⁰. When asked whether the Directive affected their organization, the majority of respondents (57%) and 94% of drug sponsors said it did. It turned out that, more than ten years after the implementation of the Directive, only a slim majority believes that the Directive has simplified and harmonized the requirements for conducting clinical trials across the EU (52%) and that the benefits of the Directive outweigh the costs (51%). Additionally, the Directive has been criticized by many sponsor organizations, both commercial and academic, for the enormous increase in administrative burdens and costs it imposes^{6, 8, 11}. In particular, the provisions of the Directive have been a financial obstacle to non-commercial trials and the conduct of independent studies⁸. The cause of the problem is considered to be the fact that the primary objective of the Directive was to facilitate commercial studies, and attention was paid to non-commercial studies only at the very end¹¹. Numerous obstacles imposed by the Directive, as well as many unresolved issues, have made the Directive arguably the most criticized document in the field of pharmaceuticals. The dissatisfaction of patients, industry, and academic institutions was expressed by creating proposals for improving the regulation of clinical trials^{12, 13}. These numerous circumstances have created the ground for a further step forward in regulating the conduct of clinical trials of drugs, and the intention is to make progress in scientific research and industry¹⁴.

Regulation 536/2014 aims to provide a competitive legal environment for the development of new drugs, especially special treatments, for instance, for rare diseases, and it is based on the need to fill regulatory gaps and establish a single framework for authorization of clinical trials that will cover all MS. The Regulation consists of 99 articles, divided into 19 chapters, plus 7 annexes⁴. Unlike the Directive, which had to be transposed into national law, the Regulation will have direct applicability within all EU MS.

Key changes of Regulation 536/2014

The new Regulation is based on three fundamental pillars: harmonization of the procedures for carrying out clinical trials due to the submission of a single e-dossier through a new information system, public disclosure of information obtained from clinical trials to increase trust and reliability, and simplified safety reporting requirements.

The objectives of the Regulation are to protect the rights, safety, dignity, and well-being of subjects, as well as

to ensure the reliability and robustness of data obtained from clinical trials, to encourage innovation and facilitate the clinical trial application process, and finally to achieve an appropriate level of transparency.

Scope and definitions

A “clinical study”⁴ is defined as any investigation in human subjects designed to: a) detect or confirm the clinical, pharmacological, or pharmacodynamic effects of one or more medicinal products; b) identify adverse reactions to one or more medical devices; c) examine the absorption, distribution, metabolism, and excretion of one or more medicinal products.

A “clinical trial”⁴ is a clinical study that meets any of the following criteria: a) the assignment of a particular treatment to a subject is predetermined and does not constitute a common medical practice in an MS; b) the decision to prescribe a study drug is taken together with the decision to include the subject in a clinical study; c) in addition to normal clinical practice, diagnostic procedures and monitoring are applied.

The scope has remained unchanged. Thus, the Regulation, as well as the Directive, does not cover the field of non-interventional studies, nor does it apply to all clinical trials conducted in the EU. However, the new Regulation introduces the concept of low-intervention trials.

“Low-intervention clinical trial” is a clinical trial that uses medical products already covered by marketing authorization, and it is involved with a minimal additional risk compared to clinical practice. Therefore, the medical product is used in accordance with the marketing authorization, or its use is supported by published scientific records⁴.

Authorization procedures

The most significant novelty is the introduction of a centralized system for reviewing and approving clinical trials. The Regulation simplifies the approval procedure via CTIS that includes the EU portal and database (EUPD)⁴. The EUPD will replace the existing European Union Drug Regulating Authorities Clinical Trials Database (EudraCT). This new information system will enable the provision of a single dossier and a single submission of the application for experimentation in all MS in which the trial will be conducted.

One of the main features of the new Regulation is a coordinated assessment between Reporting Member State (RMS) and the MS concerned, and, therefore, one single decision. The assessment will be made separately for Part I of the dossier, which represents the scientific section (level of intervention, risk/benefit for subjects, manufacturing and importation for investigated medicinal product, labeling requirements, Investigator's Brochure), and Part II of the dossier, which represents the ethics section (informed consent, subject recruitment, data protection, suitability of investigators and trial sites, damage compensation). The Part I assessment is jointly performed by MS concerned, and the assessment is coordinated by an RMS proposed by a sponsor

and approved by MS. Part II is evaluated at the national level, in each MS concerned individually and independently. There are clear timelines for the validation of the dossier, with an additional extension of deadlines given in case of need for further information. Documentation evaluations for both parts last 45 days, plus allowed clock-stop of up to 31 days (12 for response, 7 for review of responses and completion of reports). When the conclusion on Part I and Part II is finally reached, the MS have 5 days to issue a decision.

The concept of tacit approval is also established if an MS does not provide a response within a certain period.

There is a possibility that the MS does not agree with the opinion on Part I, but the disagreement can be issued only if the clinical trial is considered to be able to lead to the patients receiving inferior treatment compared to the normal practice in that MS, or in the case of infringement of national law, as well as in the case when there are concerns related to the safety of subjects, reliability and robustness of the generated data.

A refusal of an application for approval to conduct a clinical trial shall be issued if the opinion on Part I, Part II, or both is negative or if the national ethics committee has issued a negative opinion for that MS. Additionally, there is a possibility of expiration of the authorization in an MS concerned if no subject has been included in the trial within two years.

Transition period

Once the Regulation becomes applicable, there will be a three years transition period. It implies that both the old and the new application procedure for conducting a clinical trial will be parallel.

During the first year of the transition period, sponsors will be allowed to choose the way they want to submit an application – under the Directive and EudraCT database regime or the Regulation and the new IT platform regime.

In the second and third year of the transition period, all applications must be submitted via the new information system introduced by the Regulation. It is expected that all clinical trials authorized under the regime of the Directive will remain under that system, but if they are not completed by the end of the third year, they will have to be switched to the new system.

After the third year, all clinical trial applications will be governed by the new Regulation.

CTIS functionalities

As already stated above, CTIS enables the submission and management of clinical trial applications through the portal and provides communication between MS during the evaluation process. The database enables the storage of non-confidential information and makes them available to the general public.

This system is managed by the EMA, and the goal is to build interaction between this and other systems that are already under the control of the EMA.

The EMA declared public approval of the methodology and next steps regarding the plan to launch CTIS at a meeting in June 2010. CTIS has been proposed to be put into operation in December 2021 (<https://www.ema.europa.eu/en/news/highlights-management-board-june-2020-meeting>).

Transparency

One of the objectives of the new Regulation is to increase transparency regarding clinical processes and data in order to build confidence.

Article 81 (4) of the Regulation states that the EU database should be publicly accessible by default, with a few exceptions concerning: the protection of personal data, protection of commercially confidential information, protection of confidential communication between MS related to the evaluation of documentation, providing constructive oversight of clinical trials.

It is also stated that only those applications for which a decision has been made will be published and that all data and documents will be published at the first opportunity (except exceptions), with sponsors having the option to defer the timing of specific data/documents publishing. The specific data/documents include: the Investigational Medicinal Product Dossier (IMPD) quality section, draft assessment reports, names of experts, personal information about sponsor staff, personal information concerning the Marketing authorization holder/applicant, financial agreements between the sponsor and the research site, Suspected Unexpected Serious Adverse Reaction (SUSAR) and Annual Safety Reports.

Safety reporting

Given the great importance of timely and accurate safety reporting, the new Regulation has simplified safety reporting requirements to ensure the highest standards of safety for respondents.

SUSARs are presently submitted separately to all competent authorities and ethics committees of the different MS concerned, where they are assessed separately. The same applies to the Development Safety Update Report (DSUR) for an investigational medicinal product. Under the provisions of the Regulation, the sponsor will submit all SUSARs as well as the DSUR through a dedicated module of the Eudravigilance database managed by the EMA. The EMA will then forward the reports electronically to all MS concerned, and they will participate in the evaluation process.

Under the EU Directive framework, there were no requirements for reporting serious breaches of protocol, while the new Regulation stipulates that such cases should be reported within seven days. Moreover, in addition to SUSARs, it is ordered to report any unexpected adverse events with an impact on the benefit-risk ratio.

Discussion

The Regulation is a very detailed and extensive document that establishes procedures with very clearly defined deadlines. A single submission and a single decision valid throughout the EU will undoubtedly simplify the process of approving and conducting clinical trials. Accelerating these processes will greatly facilitate the work of sponsors, national regulators, and ethics committees, and improved requirements will encourage clinical research.

Additionally, the application of the new Regulation will address multiple capabilities during the planning and designing of clinical trials, their conduction, as well as during the reporting of development steps in the trial. While it is true that this entails changes in terms of roles, responsibilities, and both sponsor staff and systems competencies, there is an opportunity for standardization, process optimization, as well as education and training processes, which overall provides higher standards in medicine testing on humans.

The introduction of the category of low-intervention studies will greatly improve the investigating procedures for medicines used in accordance with the approved Summary of product characteristics, which is not regulated well enough by the current provisions. This could encourage additional trials of authorized medicines and allow those products to be used in the best possible way^{15, 16}.

The new Regulation is expected to reduce the number of redundant trials if applied adequately^{17, 18}. Redundant trials are those trials that investigate issues that may be “answered satisfactorily with existing evidence”¹⁹. Such trials are considered “unnecessary duplication of research efforts”^{20, 21} and pose an ethical problem as they unjustifiably lead to exposing the subjects to risks. For example, increased transparency, as one of the main pillars of the new Regulation, is one of the instruments for reducing wasteful research because it will disable this type of research that occurs as a result of lack of transparency¹⁷. In addition, increasing the availability of data can support academic research, strengthen the integrity of the clinical trial system, and increase public trust in this system^{15, 22}. Public disclosure of data also allows all stakeholders to access new information relevant to current and future research and is believed to be able to contribute to the protection of public health^{22–24}.

On the other hand, new and amended provisions also raise new concerns that may have a significant impact on the regulation of clinical trials. According to the SCORR Marketing and ACT survey, respondents’ opinions were divided regarding the effectiveness of the new Regulation. It was found that 51% believed that the measure would go far enough to address some of the obstacles to doing research in Europe, while 49% were not convinced. As many as 46% of respondents stated that they believed that the new Regulation would not improve the rate of applications for clinical trials in Europe¹⁰.

There are concerns that increased transparency regarding the availability of outcome data together with the availability of data related to trial participants may lead to threats to the privacy of trial participants, errors in the interpretation

of clinical trial outcomes due to inadequate data analysis, and the risk of commercially confidential data disclosures²³. An adequate balance needs to be found between the drawbacks and the advantages, and the aim of the EMA is to find an appropriate solution^{24, 25}. It is considered that the trial results should not be made publicly available until a marketing authorization has been granted²⁶.

Given that the development of clinical research goes in the direction of targeting specific groups of patients, which entails the problem of a potentially small number of subjects in studies, multicenter studies are becoming even more significant as a tool to provide a sufficient number of subjects in such studies^{27–30}. The importance of the new Regulation is reflected in the fact that the harmonization of requirements for the conduct of clinical trials across the EU sets the basis for facilitating the conduct of multicenter trials. In addition, there is no doubt that a coordinated assessment of clinical trial documentation introduced by the new Regulation provides a quality foundation for advancing research in the field of rare diseases and global epidemics, as well as innovative therapies^{15, 27}. However, the fact that the sponsor will have the right to choose an RMS (with the approval of other MS) raises concerns that only a limited number of countries will act as an RMS due to preference given to individual countries by the sponsor for various reasons²⁶.

Some provisions require extremely careful planning and synchronization. For instance, appropriate coordination will need to be established between national competent authorities and ethics committees working on assessments in parallel and within a defined timetable^{26, 31, 32}. The division of assessment tasks is an effective way to simplify the complex evaluation process but raises the issue of limiting the scope of evaluation of ethics committees only to Part II items due to its simplistic interpretation³³. As a matter of fact, the new Regulation allows MS to determine the assessment area of ethics committees³⁴. This means that they can opt for a model that involves only the assessment of Part II or a model that also includes the assessment of some Part I issues. However, it should be borne in mind that limiting the assessment process to Part II alone may have an impact on the safety of subjects in clinical trials, given the omission of some important elements in the evaluation by ethics committees, such as methodology and risk-benefit ratio. On the other hand, the current Directive requires that ethics committees also consider these aspects of clinical trials^{35, 36}. In addition, the envisaged assessment deadlines are shorter in the new Regulation compared to the Directive³⁶. Overall, adaptation to the provisions of the new Regulation will have an impact on the work of ethics committees through the introduction of changes in the existing system of evaluation processes by ethics committees. This will give rise to a thorough definition of the functioning and duties of the ethics committee within the legal framework but will also call for reorganization as well as the provision of adequate resources.

One of the issues to consider is the relocation of clinical trial sites outside the EU, particularly in Western Europe. A study by da Silva et al.³⁷ dealt with the phenomenon of globalization of clinical trials and found that the largest aver-

age increase in the number of clinical trials between 2005 and 2012 occurred in the Asian (30%) and Latin American/Caribbean (12%) regions. It was also found that the largest average annual increase in the number of clinical trials was related to the lower-middle income (33%) and low-income (21%) regions³⁷. Reasons for this trend include the burden of bureaucracy and the high costs associated with richer countries. The complexity of the demanding provisions is also considered to be a major burden in terms of compliance, documentation, and training³⁸. The new Regulation aims to stimulate the conduct of clinical trials; however, the results of the survey conducted by ACT and SCORR Marketing do not indicate the existence of high reliability in such potential of the Regulation. One of the main points of this survey is the fact that the respondents believe that in the near future, clinical trials will be largely transferred from Europe to Asia and Latin America. It is believed that clinical trials will be conducted to a greater extent in China (chosen by 46% of respondents), other Asian countries, such as Japan or North Korea (according to 40% of respondents), and Latin America (according to 37% of respondents)¹⁰.

Impact of Regulation 536/2014 on the Balkan region

The EU is becoming a more competitive market for clinical trials, including smaller EU countries that have been neglected so far due to long and complicated procedures and lack of human resources, which may reduce the Balkan region's participation in the clinical trial market.

EU members from the Balkan region (Croatia, Slovenia, Romania, and Bulgaria) will have to accept the Regulation without changes and adaptations. Countries in this region that are candidates and potential candidates for membership of the EU (Serbia, Montenegro, Bosnia and Herzegovina, and Macedonia) will have to start adapting their laws in order to be ready to introduce the Regulation without changes and adaptations.

With that in mind, it is necessary to continue to harmonize national provisions with EU regulations. On that occasion, the implementation of the highest ethical and scientific standards related to the approval, conduction, and control of clinical trials should be encouraged. It is also necessary to optimize the deadlines for approving clinical trials, as well as to increase transparency in the process of approving clinical trials.

Steps are being taken to create an appropriate basis for the development of a suitable environment for clinical trial conduction. For example, the Ethics Board of Serbia was set up in Serbia in 2019³⁹. Until then, the ethical aspects of clinical trials were assessed by the ethics committees of individual health care institutions. This approach to the regulation of clinical trials contributes to the shortening of deadlines for the evaluation of documentation and simplifying the decision-making on clinical trials approval and, consequently, to a more efficient framework for medical research involving human volunteers. Meanwhile, in Montenegro, the August 2020 law on medicines provides for the establishment of an Ethics committee of the Ministry of Health whose responsibility is to issue opinions on all clinical trials conducted in Montenegro, including multicenter clinical trials⁴⁰. The implementation of the new progressive provisions in the existing system of clinical trial documentation assessment is a great challenge but also a significant opportunity to increase the number of clinical trials as it will hopefully positively affect the sponsors' perception of clinical trials' conduction in the region.

Conclusion

Overall, the Regulation introduces new important measures that are expected to contribute to the increase in the number of clinical trials in Europe. The Regulation addresses the administrative burdens of the application process caused by redundant bureaucracy as well as the slow approval process. Although the Regulation, unlike the Directive, must be fully incorporated into national legislation, the new requirements are sufficiently broad to provide MS with sufficient flexibility in the implementation process. There are still certain barriers that need to be considered and which can burden regulatory agencies; however, the potential of the Regulation is too large to step back in the face of that challenge. The new provisions raise confidence that clinical trials will benefit greatly from the Regulation if adapted correctly. As the Regulation will have a strong impact on the requirements for clinical trials in Europe, the EMA, MS, and sponsors need to make appropriate preparations to introduce the Regulation into the clinical trial system in the best possible way. The implementation of such large measures implies the inevitable complexity, but this will ultimately result in harmonization across all EU trials and greater efficiency in achieving drug approvals.

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